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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/706,738	HILFINGER ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-16, 19, 20, 22, 24, 26, 27, and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-16,19,20,22,24,26,27 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/24/09; 6/3/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 6/3/09 has been entered.

Claims 8-16, 19, 20, 22, 24, 26, 27, and 30 remain pending and are under consideration.

Rejections and objections not reiterated from the previous Office Action are withdrawn.

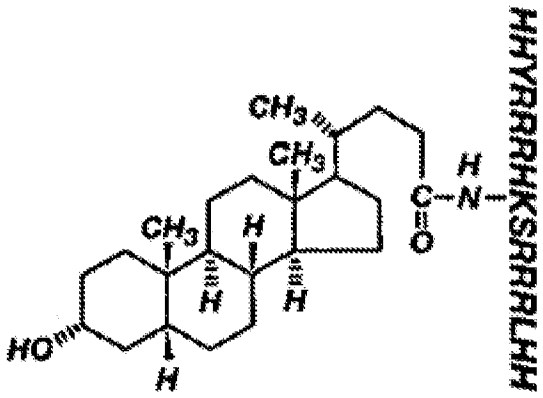
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8, 10-15, 20, 22, 26, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Mahato et al (6875611).

Mahato taught cationic lipids for nucleic acid delivery comprising a sterol or bile acid hydrophobic group conjugated to a cationic protamine peptide, such as the following structure:



A variety of hydrophobic sterol or bile acid groups could be used. Illustrative sterols included cholestanol and coprostanol. Illustrative bile acids included glycoholic acid, chenodeoxycholic acid, deoxycholic acid, glycochenodeoxycholic acid, taurocholic acid, and the like. See column 2, lines 53-62. Note that Mahato also taught that the peptide can be attached to the sterol or bile acid by peptide bond (sentence bridging columns 2 and 3), so attachment via the N terminus of the peptide is also embraced. At column 6, lines 38-44, Mahato taught that a variety of linkages could be used to attach the peptide to the hydrophobic moiety, "which can be any of a variety of linkers known in the art for linking chemical subunits together into a whole unit, such amide linkages, including peptide linkages, urethane linkages, disulfide linkages, ether linkages, and the like." Representative complexes were formulated in 5% glucose. See column 12, lines 15-18. Mahato exemplified a nucleic acid encoding IL-12, which is a secreted protein, see

column 3, lines 19-23; claim 34; and examples 6 and 7. Mahato specifically envisions local delivery to tumors in vivo at column 11, lines 3-6.

Thus Mahato anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8, 10-15, 20, 22, 26, 27, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mahato et al (6,875,611).

Mahato taught cationic lipids for nucleic acid delivery comprising a sterol or bile acid hydrophobic group conjugated to a cationic protamine peptide through C24 a discussed above, anticipating and rendering obvious claims 8, 10-15, 20, 22, 26, and 27.

Regarding claim 30, Mahato did not explicitly teach a commercial package comprising the composition and instructions for use. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to place the components of such a kit into a container. One would have been motivated to do so in order to organize the components into an easily retrievable state. One would have been motivated to include instructions because one of ordinary skill in the art appreciates that

referring to instructions decreases the frequency of errors. Thus the invention as a whole was prima facie obvious.

Claims 8, 10-15, 19, 20, 22, 24, 26, 27, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), Keener et al (US Patent 6,627,197), Gebeyehu et al (US Patent 6,075,012), and Mahato et al (6,875,611).

Niedzinski taught cholic acid conjugates comprising a substituted alkyl polyamine DNA binding domain and their use to protect DNA from degradation in the gastric system. Niedzinski envisioned the use of these conjugates to deliver therapeutic nucleic acids by oral delivery to the gastrointestinal system, particularly to the enterohepatic receptors of the small intestine, which recognize and take up bile salts. See abstract, paragraph bridging pages 721 and 722. The cholic acid moieties were esterified through an oxygen at C3 to a DNA binding domain. See scheme 1 on page 722, compounds 5 and 6. Niedzinski showed the conjugates could be used to deliver plasmids to non-gastric cells, i.e. NIH 3T3 fibroblasts (see paragraph bridging pages 725 and 726, and Fig 5 on page 726).

Niedzinski did not teach the use of cholestanol, coprostanol, glycocholic acid, chenodeoxycholic acid, deoxycholic acid, glycochenodeoxycholic acid, taurocholic acid, or taurochenodeoxycholic acid. However, Niedzinski considered his conjugation technique to be applicable to a variety of bile acids through the C3 hydroxyl (see last

sentence of column 1 on page 724). Niedzinski also did not teach DNA binding domains comprising peptides.

Keener taught the use of bile acids, and cholesterol derivatives generally, as hydrophobic conjugates to aid in the cellular entry of a conjugated peptide (a proricin variant). Proricin is hydrophilic and so does not readily traverse cell membranes. Keener overcame this problem by conjugation of a hydrophobic moiety, such as a sterol or bile acid, that facilitates traversal of the cell membrane. Disclosed hydrophobic groups included bile acids and cholesterol derivatives such as cholic acid, coprostanol, glycocholic acid, chenodeoxycholic acid, deoxycholic acid, glycochenodeoxycholic acid, and taurocholic acid. See abstract, column 4, lines 49-57, and column 19, lines 37-55.

Mahato taught cationic lipids for nucleic acid delivery comprising a sterol or bile acid hydrophobic group conjugated to a cationic protamine peptide. A variety of hydrophobic sterol or bile acid groups could be used. Illustrative sterols included cholestanol and coprostanol. Illustrative bile acids included glycoholic acid, chenodeoxycholic acid, deoxycholic acid, glycochenodeoxycholic acid, taurocholic acid, and the like. See column 2, lines 53-62. Note that Mahato also taught that the peptide can be attached to the sterol or bile acid by peptide bond (sentence bridging columns 2 and 3), so attachment via the N terminus of the peptide is also embraced. At column 6, lines 38-44, Mahato taught that a variety of linkages could be used to attach the peptide to the hydrophobic moiety, "which can be any of a variety of linkers known in the art for linking chemical subunits together into a whole unit, such amide linkages, including peptide linkages, urethane linkages, disulfide linkages, ether linkages, and the like."

Representative complexes were formulated in 5% glucose. See column 12, lines 15-18. Mahato exemplified a nucleic acid encoding IL-12, which is a secreted protein, see column 3, lines 19-23; claim 34; and examples 6 and 7.

Thus it was clear to one of ordinary skill in the art at the time of the invention that bile acids and cholesterol derivatives were recognized as exchangeable, equivalent hydrophobic groups useful for facilitating the transfer of conjugated hydrophilic groups into cells.

Gebeyehu taught reagents and methods for intracellular delivery of nucleic acids. The reagents are cationic lipids with the general formula of ABZ, wherein A is a steroid such as the bile acid cholic acid, or the sterols stigmasterol or ergosterol, B is a linker, and Z can be a nucleic acid binding domain such as a substituted alkyl polyamine (Z_4-Z_8, column 7, lines 44-67) or a polycationic peptide (protamine, a histone, or other nucleic acid binding protein). See column 9, line 62 to column 10, line 10 first, then column 3, lines 50-64; column 4, lines 50-54; column 5, lines 36 and 52-58; and scheme 8 at columns 29 and 30. Accordingly, it was clear to those of ordinary skill in the art at the time of the invention that it was routine to conjugate nucleic acid binding domains to cholesterol derivatives to make nucleic acid delivery conjugates, and that substituted alkyl polyamines and polycationic nucleic acid binding peptides such as protamines and histones were exchangeable equivalent nucleic acid binding domains.

It would have been obvious to one of skill in the art at the time of the invention to substitute any hydrophobic bile acid or cholesterol derivative for the cholic acid of Niedzinski. One of ordinary skill at the time of the invention would have had a

reasonable expectation that modified bile acids would be recognized and taken up by the appropriate receptors because Niedzinski taught that this occurred for C(3)-modified cholic acid. There is no reason of record to expect that other bile acids would not function similarly.

One of ordinary skill at the time of the invention would also have recognized that bile acids and sterols were recognized as functioning as hydrophobic moieties that can facilitate delivery of a conjugated hydrophilic moiety to cells. Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute other bile acids and sterols for cholic acid in the conjugates of Niedzinski, inasmuch as one would reasonably expect these conjugates to be taken up by the enterohepatic receptors that normally function in uptake of bile acids, and to function as transfection-facilitating hydrophobic groups even in the absence of receptors.

One of ordinary skill would recognize from the teachings of Niedzinski, Keener, Mahato, and Gebeyehu that the hydrophobic nature of the bile acid and sterol conjugates would facilitate the traversal of lipid bilayers even in the absence of a bile acid receptor (as demonstrated by Niedzinski with NIH 3T3 cells). Hence one would have had a reasonable expectation of success in substituting these equivalent hydrophobic moieties for each other. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. Furthermore, MPEP 2144.07

indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness.

It would also have been obvious to one of ordinary skill in the art at the time of the invention to substitute a nucleic acid binding peptide, such as that taught by Mahato or Gebeyehu, for the nucleic acid binding polyamine of Niedzinski because these nucleic acid binding moieties were recognized in the art as equivalents in view of the teachings of Gebeyehu, i.e. polyamines are equivalents of polycationic nucleic acid binding peptides. See MPEP 2144.06.

Regarding claims 11 and 12, it would have been obvious to deliver the IL-12-encoding nucleic acid of Mahato using the composition of Niedzinski as modified above because Mahato demonstrates delivery of the nucleic acid using a similar compound, and because nucleic acid delivery is intended purpose of the compounds of Niedzinski.

Regarding claim 20 and the 'Y' linker peptide moiety, the first 2 or 3 amino acids of the DNA-binding peptide of Gebeyehu (histone, protamine or DNA binding protein) can arbitrarily be considered to be the linker peptide.

Regarding claim 30, the cited art did not explicitly teach a commercial package comprising the composition and instructions for use. However, Gebeyehu did teach kits comprising the compositions. See column 13, lines 18-24. It would have been obvious to one of ordinary skill in the art at the time of the invention to place the components of such a kit into a container. One would have been motivated to do so in order to organize the components into an easily retrievable state. One would have been motivated to include instructions because one of ordinary skill in the art appreciates that referring to

instructions decreases the frequency of errors. Thus the invention as a whole was prima facie obvious.

Thus the invention as a whole was prima facie obvious.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), Keener et al (US Patent 6,627,197), Mahato et al (6,875,611), and Gebeyehu et al (US Patent 6,075,012) as applied to claims 8, 10-15, 19, 20, 22, 24, 26, 27, and 30 above, and further in view of Perrie et al (J. Liposome Res. 12(1&2): 185-197, 2002).

Niedzinski, Keener, Mahato, and Gebeyehu render obvious methods of delivering nucleic acids to target cells of a subject by administering a nucleic acid encoding a protein and a lipidic agent comprising a bile acid or cholesterol derivative conjugated to a polyionic DNA-binding peptide. Niedzinski taught that the DNA/lipidic agent could be formulated with DOTAP and/or DOPE and also with DMDHP and DOPE. See paragraph bridging columns 1 and 2 on page 725, Table 2 on page 726, and Fig. 5 on page 726. Gebeyehu also suggested combination of steroid derived cationic lipids with lipids such as DOPE, DOSPA, DOTMA, or cholesterol for delivery to cells (see column 5, lines 37-45).

These references did not exemplify a composition comprising an antibiotic therapeutic compound.

Perrie taught oral intragastric delivery of cationic liposome comprising nucleic acids encoding the S (small) region of the hepatitis B surface antigen (HBsAg). DNA

vaccines encoding HBsAg were formulated with a cationic lipid formulation (phosphatidylcholine/cholesterol/DOTAP) and administered orally. Immune responses against the antigen were observed. See abstract. The nucleic acid of Perrie is considered to be a therapeutic product that is antibiotic in nature by virtue of its activity in inducing an immune response against hepatitis B virus.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the conjugate of Niedzinski as modified by Keener and Gebeyehu to deliver any nucleic acid that one wished to express in a cell, regardless of the nature of the expressed protein, because the purpose of these conjugates is to deliver nucleic acids to cells. It would have been similarly obvious to use the conjugates of Niedzinski/Keener/Gebeyehu in the method of Perrie because Niedzinski and Gebeyehu taught that such conjugates could be added to cationic lipids such as DOTAP, and because the conjugate takes advantage of uptake by enterohepatic receptors. See Niedzinski at paragraph bridging columns 1 and 2 on page 725, and Table 2 on page 726, and Gebeyehu at column 5, lines 37-45. Further, Niedzinski showed in Fig. 5 that addition of a bile acid conjugate to a cationic lipid/cholesterol mixture improved transfection.

One of ordinary skill could consider the conjugates of Niedzinski, as modified by Keener and Gebeyehu, to be improved versions of the cholesterol of Perrie, i.e. versions that lend improved DNA binding and delivery characteristics, and would be motivated to substitute them for, or add them to, the cholesterol of Perrie for that reason.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), Keener et al (US Patent 6,627,197), Mahato et al (6,875,611), and Gebeyehu et al (US Patent 6,075,012) as applied to claims 8, 10-15, 19, 20, 22, 24, 26, 27, and 30 above, and further in view of Kitadai et al (Brit. J. Cancer 81(14): 647-653, 1999).

Niedzinski, Keener, Mahato, and Gebeyehu render obvious methods of delivering nucleic acids to target cells of a subject by orally administering a nucleic acid encoding a protein and a lipidic agent comprising a bile acid or cholesterol derivative conjugated to a polyionic DNA-binding peptide. Niedzinski taught that the DNA/lipidic agent could be formulated with DOTAP and/or DOPE and also with DMDHP and DOPE. See paragraph bridging columns 1 and 2 on page 725, Table 2 on page 726, and Fig. 5 on page 726. Gebeyehu also suggested combination with lipids such as DOPE, DOSPA, DOTMA, or cholesterol for delivery to cells (see column 5, lines 37-45).

These references did not exemplify expression of a therapeutic antitumoral compound in vivo.

Kitadai taught transfection of human gastric carcinoma cells with an expression vector encoding the secreted protein interleukin-8. Transfection was performed using the cationic lipid formulation LIPOFECTIN (a 1:1 mixture of DOTMA and DOPE).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the conjugate of Niedzinski as modified by Keener and Gebeyehu to deliver any nucleic acid that one wished to express in a cell, regardless of the nature of

the expressed protein, because the purpose of these conjugates is to deliver nucleic acids to cells.

It would also have been obvious to one of ordinary skill in the art at the time of the invention to use the bile acid conjugate of Niedzinski as modified by Keener and Gebeyehu in the method of Kitadai by adding it to the DOTMA/DOPE formulation (LIPOFECTIN) because Niedzinski taught that a similar conjugate could be effectively added to another DOPE/cationic lipid mixture to improve transfection (Fig. 5).

Also it would have been obvious to use a DOTAP/DOPE/conjugate mixture or a DMDHP/DOPE/conjugate mixture in place of the LIPOFECTIN in the method of Kitadai because such mixtures were intended for gene transfer to cells, and would be functional equivalents of LIPOFECTIN. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness.

The nucleic acid of Kitadai is considered to be a therapeutic product that is an antitumoral.

Response to Arguments

On 2/27/08 Applicant filed an Appeal Brief. The arguments presented therein were completely addressed in the Examiner's Answer of 4/16/08. On 6/6/08 a Reply brief was filed. The arguments presented therein are addressed below.

At page 4 of the reply brief, Applicant asserts that the Examiner's position suffers two major deficiencies.

First, Applicant asserts that one of ordinary skill in the art recognizes that Niedzinski merely teaches a chemical synthetic strategy that is applicable to multiple bile acids, but does not provide any reasonable expectation of success for substituting other bile acids since only one of two products tested by Niedzinski does not hinder the ability of cationic lipids to deliver nucleic acids to cells in vitro. Applicant refers to compounds 5 and 6, which were tested at page 725 of Niedzinski for their effects on the standard transfection reagents DOPE and DMDDHP. Compound 5 stimulated transfection, while a lower efficiency of transfection was observed in the presence of compound 6 supported transfection than in its absence. Applicant asserts that this "opposite result" means that Niedzinski's chemical synthetic scheme does not predict biological function. This is unpersuasive. The instant claims require a conjugating agent-nucleic acid complex, where the conjugating agent comprises A-R_1-Q-Z. They do not require any biological function of A-R_1-Q-Z, and do not exclude the presence of other lipids, such as DOPE/DMDDHP. Niedzinski showed successful transfection with conjugating agent-nucleic acid conjugates comprising two different cholic acid-based conjugating agents. There is no requirement in the claims that the agents must, by themselves, in the absence of any other transfection agent, provide transfection activity. All that is required is that the agents must form part of a conjugating agent-nucleic acid complex in a method of delivering nucleic acids to target cells.

Second, Applicant asserts that "if the hydrophobic nature of the C(3) functionalized cholic acid molecules were all that were required for functionality, then there would have been no need for Niedzinski to use cationic lipids to successfully deliver nucleic acid to 3T3 cells, and any hydrophobic molecule alone would be sufficient." Applicant's conclusion that Niedzinski needed to use cationic lipids to successfully deliver nucleic acid to 3T3 cells lacks evidentiary support. There is no information in Niedzinski regarding the use of compounds 5 and 6 alone to promote transfection, therefore no evidence-based conclusion can be drawn in this regard. It was the goal of Niedzinski to "increase the interaction of a lipid-DNA complex… with the terminal ileum" by adding cholic acid derivatives to the complex (page 721, right column, last paragraph).

On the other hand, each of Keener, Gebeyehu, and Mahato taught that steroid groups could be used to promote the transfer of conjugated material into cells by virtue of their hydrophobic character.

At column 19, lines 37-55, Keener states that the proricin variant for cellular delivery can be hydrophobized in order to convey the advantage of making it easier for the proricin variant to enter cells. Preferred hydrophobic agents include bile acids and sterols. Preferred bile acids include the instantly claimed glycocholic acid, chenodeoxychlic acid, deoxycholic acid, glycochenodeoxycholic acid, and taurocholic acid, as well as the cholic acid of Niedzinski. See Keener also at abstract and column 4, lines 49-59.

Gebeyehu disclosed cationic lipids and lipophilic compounds useful for making lipid aggregates for delivery of macromolecules and other compounds into cells (abstract). Hydrophobic groups included cholic acid and the sterols stigmasterol and ergosterol. These groups were conjugated to cationic groups such as cationic peptides. See column 9, line 62 to column 10, line 10 first, then column 3, lines 50-64; column 4, lines 50-54; column 5, lines 36 and 52-58; and scheme 8 at columns 29 and 30.

Mahato taught amphiphilic lipopeptides wherein the hydrophobic moiety may be cholic acid, or the instantly claimed glycocholic acid, chenodeoxycholic acid, deoxycholic acid, glycochenodeoxycholic acid, taurocholic acid, cholestanol, and coprostanol, and the like. See column 2, lines 53-62. By way of explaining how cationic lipid-mediated transfection works, Mahato indicated that it is believed that lipid anchors, such as steroids, serve to provide amphiphilic character to charged nucleic acid carriers, which would orient the head group surface charge more favorably, and also take part in hydrophobic interactions with plasma and organelle membranes. Thus Mahato supports the view that bile acids and sterols, by virtue of their hydrophobic character, support delivery of nucleic acids into cells.

In view of these suggestions and teachings by those of skill in the art, one of ordinary skill would clearly have substituted other bile acids and sterols for the cholic acid of Niedzinski with the reasonable expectation that the mere presence of the hydrophobic group would serve to facilitate cellular uptake of conjugated material. This is simply an art accepted principle of cellular delivery. The idea is analogous to that used in the general art of cationic lipid-mediated DNA transfections in which a DNA binding cationic group is attached to a hydrophobic group, such as a diacylglycerol or cholesterol moiety (e.g. DC-Chol, i.e. (cholesteryl-3(beta)N-dimethyl aminoethyl) a widely used cationic lipid transfection reagent). The conjugates of Niedzinski, Keener, and Gebeyehu are simply cationic lipids in which the hydrophobic domain is a cholesterol derivative that is a bile acid or sterol, similar to DC-Chol. In view of the teachings of Keener and Gebeyehu, one of ordinary skill in the art at the time of the invention would have reasonably expected any hydrophobic cholesterol derivative to be able to function as the hydrophobic group in a cationic lipid. Note that a prima facie case of obviousness requires a **reasonable expectation**, not a guarantee, of success. With respect to Applicant's arguments throughout the response regarding "'adequate support in the prior art' for the change in structure", and suggestion to make the specific molecular modifications necessary to achieve the claimed invention", the teachings of Niedzinski, Keener, and Gebeyehu, not to mention Mahato, make clear that those of skill readily recognized that hydrophobic moieties such as those recited in the instant claims could be expected to facilitate cellular uptake of conjugated materials. Thus

these teachings provide adequate support for the substitution suggested in the rejection to obtain specific structures embraced by the instant claims.

Applicant argues that the hydrophobic nature of the cholates of Niedzinski does not predict whether they will assist or hinder transfection. Applicant's arguments depend heavily on the observation that, while compound 5 of Niedzinski stimulated DOPE/DMDHP-mediated transfection, addition of compound 6 of Niedzinski caused a decrease in DOPE/DMDHP-mediated transfection efficiency. Based on this, Applicant asserts that a skilled artisan has no reasonable expectation that the synthetic strategy of Niedzinski will predict an ability of the product to deliver nucleic acids to cells. These arguments based on the performance differences between compounds 5 and 6 are unpersuasive. Compound 5 differed from compound 6 in the structure of the group attached to C24, where compound 5 had a methyl group and compound 6 had a $(CH_2)_{13}CH_3$ group. This difference of 13 carbon atoms is a more substantial difference than that between cholic acid, or compound 5, and any of the claimed bile acids and sterols. Thus, this single result would be insufficient to dissuade those of ordinary skill in the art from lending credence to the teachings of Keener, Gebeyehu, and Mahato regarding the feasibility of using bile acids and sterols generally to provide hydrophobic character in amphiphilic delivery compositions. Thus one of ordinary skill would have had a reasonable expectation of success in substituting other bile acids and sterols for the cholic acid of Niedzinski.

Applicant also asserts that a skilled artisan has no reasonable expectation that C(3) functionalized cholates have the ability to deliver nucleic acid at all, let alone finding that non-C(3) functionalized bile acids will have efficacy in delivery of nucleic acid to cells as demanded in the instant claims. This appears to be an argument that one of ordinary skill would not have expected the compounds of Niedzinski to promote transfection in the absence of other lipids. This is unpersuasive because the claims do not require such.

Applicant asserts at page 7 of the response that "the rejections require an unsupported leap to suggest that Niedzinski teaches that all bile acids (naturally constructed or synthetic and as a portion of a larger complex) are similarly suitable as a transfection agent toward any cell. The rejection requires no such "leap" inasmuch as the claims do not require transfection of any and all cells. Transfection of any cell type at all would satisfy this aspect of claims 8-16, 20, 22, 24, 26, 27, and 30.

Regarding the substitution of other bile acids for cholic acid and the expectation that such substitutions would yield molecules that are recognized by bile salt receptors, Applicant asserts that "[n]either Niedzinski nor the prior art of record suggests that the claimed structures will possess the same level of receptor binding or transfection efficiency absent C(3) modification." The relevance of this assertion is elusive. Whether or not "the claimed structures will possess receptor binding or transfection" is immaterial, the question is whether or not the modified structures of Niedzinski, as set forth in the rejections, would possess these characteristics. There is no requirement that the modified structures possess a level of receptor binding equal to that of ordinary bile acids or the compounds of Niedzinski.

Applicant asserts that neither Niedzinski nor the prior art of record teach or suggest the claimed list of bile acids and sterols. This is factually incorrect. As discussed in detail above and in the rejections, Keener and Mahato each suggest fictionalization of most or all of these molecules.

Applicant further argues that the results of the transfection experiments with compounds 5 and 6 of Niedzinski are contradictory, thus one of ordinary skill would have had no reasonable expectation of success in generating an agent useful for delivery of nucleic acids to cells. This is unpersuasive for the reasons set forth in detail above.

Applicant's arguments at pages 9 and 10 regarding the function of hydrophobic groups in transfection compositions are amply addressed in the discussion above and are unpersuasive because those of skill in the art generally accept the function of hydrophobic groups in transfection compositions and recognize that sterols and bile acids will function as such hydrophobic groups in those compositions.

Regarding Applicant's arguments at pages 10 and 11, the Examiner accepts that coprostanol and cholestanol could be modified at positions other than C(3), however the specification does not suggest doing so. In any case the issue has no relevance to the rejections inasmuch as it was raised only in response to Applicant's false assertion at page 8 of the Appeal Brief that the C(3) is unmodified in all members of the claimed group.

The essential points of Applicant's further arguments set forth at pages 11-13 are addressed above.

At pages 13 and 14 Applicant addresses the Perrie reference, indicating that it does not suggest the structure of the instantly claimed conjugating agents. Perrie was not relied upon for this. Perrie was relied on to teach DNA vaccines encoding HBsAg, And their oral intragastric delivery. Applicant also asserts that the antibiotic nature of Keener's compound is of no import to suggest the instantly claimed conjugating agents. This is incorrect. As discussed at length above, Keener taught that conjugating a hydrophobic group, such as a sterol or bile acid, to a compound can aid cellular uptake of the compound.

Applicant addresses the rejection of claims 11, 12, 15, and 16 at pages 14 and 15 of the response, but the issues raised therein are addressed in detail above. Niedzinski clearly indicates that the purpose of synthesizing the disclosed compounds was to supplement existing transfection systems. Accordingly it would have been obvious to add the compounds of Niedzinski, as modified, to other transfection systems such as DOTMA/DOPE or DOTAP/DOPE.

For these reasons the rejections are maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Richard Schnizer/
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